REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on January 14, 2004. Claims 1-7, 9-12, 14-27, and 29-56 are pending.

Applicants note, with appreciation, the indication that Claims 6, 21, 24, 36, 47, 48 and 56 would be allowable if rewritten in independent form.

Claim amendments were made to better define one embodiment of the invention, notwithstanding the Applicants' belief that the unamended claims would have been allowable, without acquiescing to any of the Examiner's arguments, and without waiving the right to prosecute the unamended (or similar) claims in another application, for the purpose of furthering Applicants' business goals and expediting the patent application process in a manner consistent with the PTO's Patent Business Goals. None of the amendments to the claims is related to the statutory requirements of patentability unless expressly stated so herein. Applicants reserve the right to prosecute the originally filed claims in the future.

Rejections under 35 U.S.C. §112

Claim 9 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and claim the invention. More specifically, the Office has noted that the dependency should be clarified. Applicants have amended claim 9 herein; it now depends on claim 7 rather than claim 8. Applicants request that the rejection be withdrawn.

Rejections under 35 U.S.C. §102

Claims 1, 7, 10-12, 14-16, 22, 23, 25-27, 29-31, 37-42, and 49-55 have been rejected under 35 U.S.C. §102(e)(2) as being allegedly anticipated by Giuliano et al. U.S. 6,416,950 ("Giuliano"). Applicants respectfully traverse this rejection.

Giuliano is cited as describing the optical analysis of cells for evaluating compounds that affect particular biological function. The Office highlights the description in Giuliano of the analysis of two related but genetically different or modified

mouse cell lines. In addition, the Office cites to Column 76, lines 45-51 to support a broadening of the analysis from mouse cell lines to any cell type, including fungi.

Applicants respectfully disagree with the Office's interpretation of Giuliano and maintain that the cited art does not anticipate the claimed invention. Specifically, Applicants maintain that Giuliano does not teach or suggest the analysis of two related but genetically different or modified mouse cell lines. The analysis cited by the Office was performed on mouse connective tissue fibroblasts (L-929; ATCC CCL-1) and a highly invasive glioblastoma cell line (SNB-19; ATCC CRL-2219). However, according the ATCC website (copy enclosed), the latter cell line is a human cell line rather than a mouse cell line. As such, Giuliano *compares a human cell line to a mouse cell line*. Giuliano does not teach or suggest the analysis of two related but genetically different cell lines as claimed herein.

Moreover, Giuliano describes "fluorescent-protein biosensors", i.e., a class of luminescently labeled macromolecules designed to sense and report environmental changes that occur either internally or on a surface. However, Giuliano only provides examples of such biosensors for *use with mammalian cells*. Giuliano does not teach or suggest how to use such sensors in fungal cells as claimed herein.

As Giuliano does not teach or suggest the claimed invention, Applicants respectfully request that the rejection be withdrawn.

<u>Rejections under 35 U.S.C. §103</u>

Claims 1-5, 7, 10-12, 14-20, 22, 23, 25-27, 29-35, 37-46, and 49-55 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Giuliano in view of Winzeler et al. (1999) Science 285:901 ("Winzeler").

A *prima facie* case of obviousness requires the Examiner to cite to a reference (or combination of references) which (a) discloses all the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine or modify those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out (*See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988)). Failure to establish **any**

one of these three requirements precludes a finding of a *prima facie* case and, without more, entitles Applicant to allowance of the claims at issue. As stated in *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988):

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art . . . . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.

Applicants assert that the cited references, either alone or in combination, do not teach the presently claimed methods.

Giuliano has been discussed above. The Office has cited Winzeler for its description of the usefulness of yeast. However, Winzeler does not teach or suggest the use of image-based methods for the analysis of a collection of genetically modified cell strains that are congenic with a parent strain. Further, Winzeler does not teach or suggest the use of fluorescent reporter molecules to analyze such cells. As such, Winzeler does not rectify the deficiencies of Giuliano.

As the references, either alone or in combination, do not teach the presently claimed invention, Applicants assert that by suggesting that the cited art may be used to produce the methods of the presently claimed invention, the Examiner presents, in essence, an "obvious to experiment" or "obvious to try" standard for obviousness. The "obvious to try" standard has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where "the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful" (quoting *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 [Fed. Cir. 1988], *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 [Fed. Cir. 1989]). There is no teaching in either of the cited references regarding methods to analyze yeast strains using the

methods claimed herein. Thus, there is simply nothing in the cited prior art that would provide one of ordinary skill in the art with the knowledge necessary to develop such methods (*i.e.*, with the parameters and elements necessary to successfully conduct the presently claimed methods).

Applicants respectfully request that the rejection be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: March 26, 2004

By: _____
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Misidentified Cell Lines

As a result of implementing DNA analysis as part of our routine quality control procedures, ATCC has discovered that some lines (see below) are not as originally reported. Current DNA profiling analyses use the GenePrint PowerPlex 1.2 system and STR loci D16S539, D7S820, D13S317, D5S818, CSF1PO, TPOX, TH01, vWA, and amelogenin.

Inappropriate Y – DNA profiling at ATCC for amelogenin, a sex-chromosome-specific PCR* assay that can distinguish X chromosome-specific products from Y chromosome-specific products revealed the presence of Y chromosomes in six human cell lines of putative female origin. Confirmation of the general findings was accomplished by QM staining, C-banding, and FISH, with a whole chromosome paint probe to the human Y chromosome.

The cell lines Include:

Designation	ATCC number	Cytogenetic Confirmation
OV-1063	CRL-2183	QM, C, FISH
CHP-234	CRL-2272	
NCI-H738	CRL-5839	QM, C, FISH
NCI-H1514	CRL-5873	QM, C, FISH
NCI-H1622	CRL-5880	
HBL-100	HTB-124	QM, C, FISH

ATCC intends to discontinue distribution of these lines unless there are compelling reasons to resume supply.

Identities in Question:

SNB-19 (ATCC CRL-2219) and U-373 MG (ATCC HTB-17) – DNA profiling at ATCC reveals that SNB-19, a human glioblastoma cell line has a STR pattern identical to that for U-373 MG (ATCC HTB-17). SNB-19 and U-373 MG also share derivative chromosomes. These observations were confirmed with the original stock available to ATCC. Distribution of SNB-19 will be discontinued.

U-118 MG (ATCC HTB-15) AND U-138 MG (ATCC HTB-16) – Two human glioblastoma lines reportedly from different individuals have identical VNTR and similar STR patterns and karyotype. U-118 MG and U-138 MG are very similar cytogenetically and share at least six derivative marker chromosomes. ATCC will continue distribution with an alert that the two lines have similar origin.

U-373 MG (ATCC HTB-17) – As a result of gene sequencing the authenticity of HTB-17 has been questioned by R.F. Petersson in Stockholm and collaborator E.G. Van Meir in Atlanta (personal communication and see Ishii, N., et al. Brain Pathol 9: 469-79, 1999). They report similarities between U-373 MG (HTB-17) and another glioblastoma, U-251. The cell line U-373 MG, obtained from the original lab in Uppsala has differing genetic properties from the ATCC HTB-17 (U-373 MG).

ATCC intends to investigate the matter further and will temporarily halt distribution of HTB-17.

ECV-304 – The German Cell Culture Collection (DSM) inquired of ATCC and the other national cell banks about the presumptive endothelial line ECV-304 and the human bladder line T24, suggesting that ECV-304 was a derivative of T24. Our DNA profiling studies revealed STR patterns that were very similar. Furthermore, ATCC karyotypes of the two lines show two shared-marker chromosomes. Combined, these results show that ECV-304 is indeed a derivative of T24, a line that was developed years earlier.

It is important to emphasize that all stocks of ECV show similar properties, not just those from ATCC. It is clear that the contamination took place **before** the cell banks independently received initial stocks. ATCC has written to each recipient of ATCC CRL-1998 (ECV-304) to inform them of these findings. At least four laboratories have reported back that ECV showed some biomarkers expected of endothelial cell lines, namely Factor VIII, tubule formation on Matrigel, and/or Weibel-Palade bodies. Studies to determine if T24 exhibits any such markers are underway.

As additional lines are discovered we will report these general findings on this page after the originators and other cell resource banks have been informed.

*The Polymerase Chain Reaction (PCR) process is covered by patents owned by Hoffmann-La Roche, Inc. Its use requires a license.

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